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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,953	07/11/2001	Achim H. Krotz	ISIS-4797	9234

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/13/2002

07

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,953	KROTZ ET AL.	
	Examiner	Art Unit	
	James D. Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is directed to formulations comprising modified oligonucleotides or their bioequivalents, wherein said formulation comprises said modified oligonucleotides or their bioequivalents and an antioxidant in a bi-phasic or multi-phasic solution, wherein said antioxidant partitions into the aqueous phase.

The specification as filed contains a definition for the term "bioequivalents" as that which encompasses any pharmaceutically acceptable compound of the present invention wherein administration of such provides "for the biologically active metabolite or residue". Although the specification provides several non-limiting examples, it does provide any real limits as to what such compounds are. Further, one cannot ascertain what the "biologically active metabolite or residue" refers to since neither the claims nor said definition disclose an intended function or use of said bioequivalents. Since applicant has described neither structure nor function of said bioequivalents, the skilled artisan would not have been able to envision what it is that constitutes

a bioequivalent as claimed in the instant application. Thus it appears that applicants were not in possession of the claimed entities at the time of filing.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim1-5, 7-12 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al. (U.S. Patent 6,258,600).

The invention of the above claims is directed to formulations comprising oligonucleotides with base, sugar, linkage and 2' modifications and an antioxidant in bi- or multi-phasic solution, wherein said antioxidant partitions to the aqueous phase.

Zhang et al. teach oligonucleotides with base, sugar, linkage and 2' modifications. Zhang et al. teach that these compounds can be prepared in a bi-phasic emulsion, and that antioxidants are commonly added to emulsion formulations to prevent deterioration of the formulation. Further, Zhang et al. teach the use of water soluble antioxidants such as ascorbic acid which have the inherent property of segregating to the aqueous phase in bi-phasic solutions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modi et al., in view of Zhang et al., Burt et al., and Baracchini et al.

The claims of the instant invention are drawn to formulations comprising oligonucleotides with base, sugar, linkage and 2' modifications and an antioxidant in bi- or multi-phasic solution, wherein said antioxidant partitions to the aqueous phase, or methods of preventing desulfurization wherein said antioxidant is added to said formulation.

Modi et al. teach pharmaceutical preparations comprising bi-phasic solutions that contain antisense oligonucleotides and water-soluble antioxidants such as ascorbic acid to prevent degradation and oxidation of the pharmaceutically active ingredients and the inherent method of adding said antioxidant to prevent said degradation and oxidation. Modi et al. do not teach phosphorothioate, base, sugar, linkage and 2' modifications, or the use of cysteine, glutathione, α-lipoic acid, 2-mercapto-5-benzimidizole salt or 2-mercaptoethanesulfonic acid as antixidants.

Zhang et al. and Baracchini et al. teach antisense compounds comprising phosphorothioate, base, sugar, linkage or 2' modifications.

Burt et al., teach the addition of imidizole derivatives to antisense nucleotides in order to reduce oxidation.

It would have been obvious to one of ordinary skill in the art to incorporate the modifications of Baracchini et al. or Zhang et al. into the antisense oligonucleotides of Modi et al. and to use antioxidants in pharmaceutical compositions thereof as taught by Burt et al., because Baracchini et al or Zhang et al. teach that said modifications of oligonucleotides increase their permeability, half-life, and resistance to degradation, and since Modi et al. teach that those skilled in the art will recognize that is "usual" to add at least one antioxidant to pharmaceutical preparations in order to decrease degradation and oxidation. One of ordinary skill in the art would have had a reasonable expectation of success in modifying said oligonucleotides and in

using antioxidants to prevent oxidation, since Baracchini et al. or Zhang et al. clearly describe how such modified oligonucleotides are made and such modifications are routinely performed by those in the art, and since the use of antioxidants is well known in the pharmaceutical art as demonstrated by Burt et al. Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James D. Schultz, PhD
June 12, 2002

ANDREW WANG
PRIMARY EXAMINER